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TITLE: Improving Symptom Control, QOL, and Quality of Care for Women with Breast Cancer: Developing a Research Program on Neurological Effects Via Doctoral Education

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13. ABSTRACT (Maximum 200 Words)

The **purpose** of this traineeship is to develop the academic and research skills of an expert advanced practice nurse towards achieving the career goal of becoming a Clinical Breast Cancer Research Scientist. In conjunction with the doctoral program, through a mentored research experience Ms. Bakitas is expanding an established research program on CNS effects of breast cancer treatment by developing a parallel focus on the peripheral nervous system effects of chemotherapy, (Chemotherapy-Induced Peripheral Neuropathy [CIPN]), on quality of life.
The major **achievements** of the trainee at this **annual report** are successful accomplishment of the planned training activities/tasks originally outlined for the second year, with an additional achievement of ongoing participation as a consultant in a funded neuropathic pain grant, abstract presentations, acceptance of doctoral proposal and acquiring an ACS doctoral scholarship. The significance of these achievements is that the training has provided for ongoing development of a clinical nurse expert towards development of a program of breast cancer research.

14. SUBJECT TERMS
Cancer control, outcomes research, quality of life, symptom management, neurological effects, doctoral education

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Introduction

This is the second year of a training grant that proposed an interdisciplinary, mentored, clinical research experience on the understudied area of neurological effects of breast cancer treatment through a doctoral training program. A no cost extension was granted thus extending the grant period to 14 May 06 (Months 25-36). Hence this annual report will summarize the accomplishments of Months 13-24 and will describe the anticipated work of the extension period (Months 25-36). A revised Statement of Work (revisions appear in bold) reflects the activities of the extension and has been modified slightly based on findings from the previous year's work (described below). The revised statement has been submitted (4/20/05) for approval to Ms. Kimbark and is included (in addition to the original statement of work) as Appendix A.

The purpose of this traineeship is to develop the academic and research skills of the trainee within the context of a doctoral nursing program and the mentor's funded program of research on (central nervous system) Cognitive Effects of Chemotherapy. The traineeship supports Ms. Bakitas in the long term career goal of developing as a Clinical Breast Cancer Research Scientist. Ms. Bakitas is expanding the Center for Psycho-oncology Program's focus on Central Nervous System/Cognitive Effects of Chemotherapy, by developing an independent, but related focus on the peripheral nervous system effects of chemotherapy (Chemotherapy-Induced Peripheral Neuropathy [CIPN]) on quality of life. Ms. Bakitas has made significant progress in accomplishing tasks described in the original statement of work. As a result of the findings from the first year and the approved dissertation proposal, the Statement of Work has been revised to focus on the understanding the symptom experience and quality of life effects from the perspective of the patient; a specific gap revealed through the past year's review of literature.

The traineeship continues to be based at two campuses: the Dartmouth Medical School/Norris Cotton Cancer Center, Lebanon, NH and Yale University, New Haven, CT. The trainee's research mentor, Tim Ahles, PhD, Director of Psycho-oncology Research, Norris Cotton Cancer Center supervises the trainee's clinical research skill development at Dartmouth. Professor Ruth McCorkle, PhD and dissertation chair, Tish Knobf, RN, PhD supervise the academic and research components at Yale University.

Body

This section is organized according to the Tasks listed in the revised Statement of Work (Appendix A). Achievements are reviewed and summarized for each of the original three tasks.

Task 1. Develop research skills and abilities, including measurement, data analysis, and conceptual model development in breast cancer research through mentorship and doctoral education. (Months 1-18)

The trainee successfully completed all of the proposed tasks according to the timeline. This was summarized in the accepted 03-04 report Tasks 1.a and 1.b are ongoing throughout the grant period. Tasks 1.f was completed in Dec. 04 when the trainee successfully defended her proposal and passed the Qualifying Exam. Task 1.g, study initiation occurred as of 1 April 05 with scientific review and IRB approval of the study. Task 1. h Dissertation advisement commenced in Summer 04 (see Transcript –Appendix

C) and will continue until successful defense of the dissertation, currently planned for April 06.

Task 2. Collect pilot data on chemotherapy-induced peripheral neurological (CIPN) effects in conjunction with serial neuropsychological and quality of life measures in women enrolled in a longitudinal study of cognitive effects of breast cancer treatment (Months 1-24; extension Months 25-36).

The trainee proposed a series of steps to understand the foundational theoretical, instrumental, and clinical skills necessary to perform appropriate assessment of chemotherapy-induced peripheral neuropathy (CIPN). A major finding from the empirical literature review Task 3a. (Bakitas, Smith, Cohen, & Fadul, 2004) (see Abstract –Appendix B) and consultation with neurological experts demonstrated a lack of consensus or gold standard in physical assessment and self-reported CIPN and quality of life. The multidisciplinary expert panel/project team composed of Dartmouth consultants (Cohen/Fadul/Smith) considered proposing a pilot study to validate a neuropathy tool modified for use in CIPN (the "reduced" Total Neuropathy Score (TNS) (Cavaletti et al., 2003; Chaudhry, Chaudhry, Crawford, Simmons-O'Brien, & Griffin, 2003). However, further study revealed basic flaws in the ability of this new tool to elicit a patient-based understanding of symptoms and quality of life information. Therefore, the trainee has focused the dissertation proposal on addressing this gap in our current understanding of chemotherapy-induced neuropathy. (See further development of this under Task 3).

Per Task 2.c, the FACT-TAXANE was added to the serial measures conducted in two of the mentor's breast cancer studies: (Ahles) A Prospective, Longitudinal Study of the Cognitive Effects of Chemotherapy, and (Ahles/Saykin): Neural Mechanisms of Chemotherapy-Induced Cognitive Disorder. Recruitment is complete on the former study; data will be available on 67 breast cancer patients who have completed baseline, 1 month, 12 month, and 24 month questionnaires. The latter study is in an early stage and recruitment of 50 women receiving chemotherapy is planned. Preliminary analyses of the neurotoxicity data from the FACT is planned during the extension year. A very preliminary review of some completed questionnaires indicates less indication of neurotoxicity as rated in the questionnaire than is apparent in medical record review of these same women. Such discrepancy is what the current study will attempt to address.

Task 3. Identify gaps in knowledge, research hypotheses, and feasible methods to study and develop interventions as a basis for a doctoral dissertation and future program of research (Months 6-24; extension Months 25-36).

The trainee has been extremely productive in this area. The ongoing literature review (updated citations compiled in Appendix F) in conjunction with the Instrument Development Workshop and dissertation advisement provided the scientific basis for continuing development of the conceptual models, dissertation proposal and other activities related to the study of CIPN. The models (included in Appendix D and E) were reviewed and critiqued by the expert panel (Fadul/Cohen/DeLeo) and will next undergo modification based on empirical data from the dissertation.

A variety of activities occurred in relation to Task 3. f:

(1) The trainee attended three conferences in the preceding year that contributed to knowledge, research networking and dissertation proposal development: 1). July 19-

24- University of North Carolina-"Instrument Development"; 2). International Association for the Study of Pain (IASP) Special Interest Group on Pain Conference "Mechanisms and Treatment of Neuropathic Pain" November 4-6, 2004; and 3). 8th National Conference on Cancer Nursing Research, February 3-5, 2005. An abstract representing the trainee's review of 45 cancer chemotherapy trials (1980-2004) that measured and reported CIPN was developed and submitted to the latter two conferences as well as locally at the 19th Annual Neuroscience Day at Dartmouth Medical School. The abstract was accepted for poster presentation at each forum, and received a 2nd place award at the Cancer Nursing Research Conference in the "Doctoral Student" division.

(2) As a consultant of the ONS Neuropathic Pain Outcomes Grant (described last report) the candidate has prepared and presented a lecture and training session for nurse practitioners to improve their assessment and examination skills in neuropathy and neuropathic pain. This is available on the Norris Cotton Cancer Center website. A related presentation, co-presented with expert, Joyce Deleo, PhD was published in January 2005 in CD Rom format for "Nurses-Digest Medical-Surgical Nursing".

(3) As a result of research conferences networking on the topic of CIPN two additional activities have occurred: Ms. Bakitas was asked to prepare a summary of "Neurological Effects of Cancer Treatment" for the Oncology Nursing Society Research Agenda (2005-2007); and she also reviewed an evidence-based guideline on chemotherapy-induced peripheral neuropathy to be published on-line on the ONS site.

Task 3.g was completed (passing of Qualifying Exam) with successful preparation and defense of the dissertation proposal in Dec 04. The purpose of this exploratory, descriptive study is to explore, understand and describe the symptoms and quality of life issues that result from neurotoxic chemotherapy agents' effect on the peripheral nervous system. Patients' descriptions through open-ended, semi-structured interview will be the primary means used to understand the experience of living with CIPN (See Appendix G- Study Brochure).

The primary specific aims of the study are to:

1). Describe the CIPN symptom experience from the patient's perspective;

2). Explore and describe the patient's experience of living with CIPN.

This investigation will contribute to understanding and likely measurement/ instrument refinement and /or development.

Key Research Accomplishments

- Completed doctoral coursework
- Passed Qualifying Examination
- Dissertation proposal completed, accepted by doctoral dissertation committee
- Dissertation proposal approved by Yale University and Dartmouth-Hitchcock Scientific Review and Human Subjects committees
- Dissertation study underway-April 2005
- Continued consultant role on funded research project on CIPN
- Synthesized and Presented CIPN literature for dissertation proposal, 3 accepted poster abstracts, and a manuscript in progress.

- Compiled and Presented "Neurological Effects of Cancer Treatment" Oncology Nursing Society Research Agenda (2005-2007)-To be published 5/05.
- Reviewer for "Chemotherapy-Induced Peripheral Neuropathy" an Oncology Nursing Society on-line evidence based guideline.
- Achieved American Cancer Society Doctoral Dissertation Scholarship (funding available 9/05-9/06)

Reportable Outcomes

The trainee has continued to participate as a consultant on a Neuropathic Pain funded research grant, and has contributed to national organizations CIPN-related science via serving as a contributor on Neurological Effects portion of the 05-07 ONS research agenda and as a reviewer of a soon to be released evidence-based guideline on CIPN. Poster abstracts, describing the foundational work of the dissertation related to measurement issue of CIPN, were accepted for presentation at international, national, and regional scientific meetings. A manuscript describing this in-depth analysis is being prepared for a peer-reviewed multidisciplinary journal. Lastly, the trainee has received notice of qualification for an American Cancer Society Doctoral Scholarship.

Conclusions

Through this training grant Ms. Bakitas has developed an independent doctoral dissertation proposal that is now underway in an understudied area of breast cancer research, namely chemotherapy-induced peripheral neuropathy. This study examines the patient's symptom experience of CIPN and its impact on quality of life. This research will contribute to an understanding of this dose-limiting effect that can significantly interfere with cancer treatment and quality of life. Furthermore, through this mentored, research training program, the trainee has made significant progress in developing a future career in clinical breast cancer research. This information will be presented this June at the Era of Hope Conference.

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Bakitas, M. A., Smith, E., Cohen, J., & Fadul, C. (2004, November 4-6). *Measurement issues in chemotherapy-induced peripheral neuropathy.* Paper presented at the International Conference on the Mechanisms and Treatment of Neuropathic Pain, Bermuda.

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Chaudhry, V., Chaudhry, M., Crawford, T., Simmons-O'Brien, E., & Griffin, J. (2003). Toxic neuropathy in patients with pre-existing neuropathy. *Neurology, 60*, 337-340.

Oncology Nursing Society. (2003). *Oncology Nursing Society: Research Agenda 2003-2005*. Pittsburgh, PA: Oncology Nursing Society.

Appendices

A. **Statement of Work**
Revised Statement of Work

B. **Poster Abstract Presented at the 7th International Conference on Neuropathic Pain, Bermuda (11/04), at the 8th National Conference on Cancer Nursing Research, Ft. Lauderdale, FL and at the 19th Annual Neuroscience Day, DHMC, (2 /05)**

C. **Transcript**

D. **Conceptual Model of Trajectory of Neurological Effects**

E. **Conceptual Model of CIPN Effects on QOL**

F. **Updated Literature Review for Dissertation Proposal**

G. **Recruitment Brochure for CIPN study**

Statement of Work

This statement of work provides an overview of a two year project in which the candidate will spend half of her week on the Yale Campus and half on the Dartmouth Campus.

Task 1. Develop research skills and abilities, including measurement, data analysis, and conceptual model development in breast cancer research through mentorship and doctoral education. (Months 1-18)

1. Weekly meeting with Dr. Ahles for mentored research supervision (Months 1-24)
2. Participate in 15 hrs/wk supervised Research Activities with doctoral faculty (Month 1-18)
3. Complete Year 1-Spring term (Months 1-5) and Year 2 –Fall and Spring (Months 9-17) required doctoral coursework (Yale)
4. Take Research Methods (CECS), Neurology, or Pharmacology Cognates (DMS) (Months 1-5, 9-12, 13-17)
5. Complete Preliminary Exam (at completion of 1st year of coursework) Month 6
6. Complete Qualifying Exam (at completion of 2nd year of coursework) Month 18
7. Dissertation underway (Month 21-completion)
8. Dissertation advisement (Month 21-completion)

Task 2. Collect pilot data on peripheral neurological (PN) effects in conjunction with serial neuropsychological and quality of life measures in women enrolled in a longitudinal study of cognitive effects of breast cancer treatment. (Months 1-18)

1. Precepted Clinical Neurological Examination Skills (Cohen/Fadul) (Months 1-3)
2. Precepted Neuropsychological Assessment Training (Ahles)
3. Refine and produce standardized neuropathy assessment tool (Cohen/Fadul) (Month 1-5)
4. Develop PN Data Management Procedures (Month 5)
5. Attend weekly meetings of Psychooncology Center for Research and Breast Cancer Tumor Board to identify breast cancer patients on study (Months 6-18)
6. Perform neuropathy assessment on breast cancer patients enrolled in Longitudinal Cognitive Effects (Months 6-18)

Task 3. Identify gaps in knowledge, research hypotheses, and feasible methods to study and develop interventions as a basis for a doctoral dissertation and future program of research (Months 6-24)

1. Perform Review of Literature on Neurological Effects (Months 6-9)
2. Perform Secondary analysis of existing data and summarize preliminary data (months 6-9)
3. Develop draft of a model of neurological effects of breast cancer treatment (Month 10)
4. Call expert panel meeting (Month 10 & 17)
5. Incorporate expert panel comments into model (Month 11-12)
6. Generate list of problems/hypotheses and methods to study, determine feasibility of conducting studies of above, determine funding sources, develop patient educational materials on CNS/PNS effects (Months 12-18)
7. g. Develop dissertation defense based on above to prepare for qualifying exam (Months 12-18)

Revised Statement of Work (4/20/05 to completion 5/06)

This statement of work provides an overview of a two year project in which the candidate will spend half of her week on the Yale Campus and half on the Dartmouth Campus. **A no-cost extension has been granted revising the statement of work to cover an additional year through 5/06).**

Task 1. Develop research skills and abilities, including measurement, data analysis, and conceptual model development in breast cancer research through mentorship and doctoral education. (Months 1-18)

a. Weekly meeting with Dr. Ahles for mentored research supervision (Months 1-24)
   b. Participate in 15 hrs/wk supervised Research Activities with doctoral faculty (Month 1-18)
   c. Complete Year 1-Spring term (Months 1-5) and Year 2 –Fall and Spring (Months 9-17) required doctoral coursework (Yale)
   d. Take Research Methods (CECS), Neurology, or Pharmacology Cognates (DMS) (Months 1-5, 9-12, 13-17)
   e. Complete Preliminary Exam (at completion of 1st year of coursework) Month 6
   f. Complete Qualifying Exam (at completion of 2nd year of coursework) Month 18
   g. Dissertation underway (Month 21-completion)
   h. Dissertation advisement (Month 21-completion)

Task 2. Collect pilot data on peripheral neurological (PN) effects in conjunction with serial neuropsychological and quality of life measures in women enrolled in a longitudinal study of cognitive effects of breast cancer treatment. (Months 1-18)

   a. Precepted Clinical Neurological Examination Skills (Cohen/Fadul) (Months 1-3)
   b. Precepted Neuropsychological Assessment Training (Ahles)
   c. Revised: Incorporate FACT-TAXANE (neuropathy assessment) into Cognitive Studies (Months 10-26) and review preliminary data (Months 28-36)
   d. Review literature on neuropathy assessment (Cohen/Fadul/Smith) (Month 12-18)
   e. Evaluate CIPN measurement methods for use in dissertation proposal (Month 12-24)
   f. Submit Abstracts (Month 18) on measurement methods and develop manuscript for publication (Month 18-27).
   g. Develop PN Data Management Procedures (Month 5)
   h. Attend weekly meetings of Psychooncology Center for Research and Breast Cancer Tumor Board to identify breast cancer patients on study (Months 6-18)
   i. (Revised and incorporated this task into 2.c above) Perform neuropathy assessment on breast cancer patients enrolled in Longitudinal Cognitive Effects (Months 6-18)

Task 3. Identify gaps in knowledge, research hypotheses, and feasible methods to study and develop interventions as a basis for a doctoral dissertation and future program of research (Months 6-24 **and extension Months 25-36)**

   a. Perform Review of Literature on Neurological Effects (Months 6-9)
   b. Perform Secondary analysis of existing data and summarize preliminary data (months 6-9)

c. Develop draft of a model of neurological effects of breast cancer treatment (Month 10)
d. Call expert panel meeting (Month 10 & 17)
e. Incorporate expert panel comments into model (Month 11-12)
f. Generate list of problems/hypotheses and methods to study, determine feasibility of conducting studies of above, determine funding sources, develop patient educational materials on CNS/PNS effects (Months 12-18)
g. . Develop dissertation defense based on above to prepare for qualifying exam (Months 12-18)
h. Perform on-going and final analysis of data from dissertation: (Months 25-36).
i. Dissertation defense: (proposed for Month 36).

MEASUREMENT ISSUES IN CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY (CIPN)

Marie Bakitas, MS, ARNP , Ellen Smith, MSN, ARNP, Jeffery A. Cohen, MD, Camilo Fadul, MD

ABSTRACT

Purpose: To describe and compare characteristics, reliability, and validity of various objective and subjective measures of chemotherapy-induced peripheral neuropathy (CIPN) used in cancer clinical trials.

Background/Significance. CIPN is a derangement in structure and function of peripheral nerves caused by chemotherapy. CIPN is an understudied side effect that can cause significant functional and quality of life impairments. Although, other chemotherapy toxicities have been minimized or eliminated (e.g. anemia, neutropenia, nausea/vomiting), CIPN remains a dose-limiting toxicity. However, CIPN presents clinical and research challenges because of its variable presentation, course, pattern of effects, and measurement issues. Clinician judgment, patient tolerance, and "objective" grading systems are used to determine when dose limits are reached.

Methods: A MEDLINE search of CIPN measures and clinical trials from 1980-October 2004 (N=58 citations) was conducted.

Results: Forty-five articles reporting instrument psychometrics and chemotherapy trials were reviewed and summarized. Studies that evaluate CIPN have traditionally used clinician grading systems (e.g. NCI-Common Toxicity Criteria, WHO, ECOG). Other evaluations included nerve biopsy, neurological examination, quantitative sensory testing (QST), nerve conduction studies (NCS), self-report scales, and composite measures which combine subjective, objective and quantitative tests (e.g. Total Neuropathy Score (TNS). Some self-report measures also include a quality of life component.

Conclusions: CIPN measurement lacks consistency across trials and there is no consensus on a "gold standard". Additionally, inter-scale and intra-scale reliability and validity varies. Most scales were developed with limited patient derived qualitative data. As a result it is difficult to evaluate how well these measures capture the clinically relevant patient experience.

Implications: Lack of CIPN measurement precision may lead to under-recognition and under-treatment of potentially dose-limiting chemotherapy toxicity. Evaluation of current measurement techniques reveals the lack of standardization and inadequacies of judging clinically relevant patient experience. A qualitative inquiry (in progress) of the patient's experience and functional status could inform clinicians about the patient's experience and may enhance CIPN instrument reliability and validity.

METHODS

Literature reviews for two data sources included:

1) **CIPN Measures**
- Ovid MEDLINE, hand search of references, personal communication with investigators

2) **Chemotherapy Trials Reporting CIPN**
- Ovid MEDLINE, CINAHL search (search terms: chemotherapy, clinical trials, peripheral neuropathy; and limited to English language, 1980-October 2004) yielded 59 citations. Additional sources included reference lists, web sources, and personal communication with investigators.

- Research reports met the following criteria:
  - 1) original report of chemotherapy trial or trial to test agents to prevent or reduce CIPN;
  - 2) peripheral neuropathy noted;
  - 3) CIPN measures described.

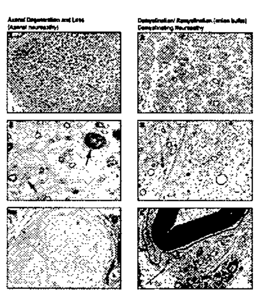
- Studies were summarized on a table under the following headings: Study author/ year; Sample; Chemotherapy Drugs; Measures; CIPN Incidence/Results.

CIPN MEASURES - SUMMARY

Table 1. Objective Measures to Evaluate CIPN

Measure	Validity	Reliability	Sensitivity/ Specificity	Comments
Nerve Biopsy (see Figures 1 & 2)	N/A	N/A	Not for CIPN	To describe mechanisms
Nerve Conduction Studies EMG		Not in CIPN		Costly equipment Patient tolerance MD must do Does not correlate w/ clinical degree of CIPN
Quantitative Sensory Testing (QST) -light touch/pressure -vibration -thermal sensory thresholds -heat/cold thresholds	inconsistent	Not in CIPN		Costly equipment Technician/clinician can do Does not correlate w/ clinical degree of CIPN
Vibration Perception Threshold				
128 Hz Tuning Fork	•	Interrater	•	
CASE IV WR Electronics Minneapolis, MN	•		•	
Vibrameter SOMEDIC Stockholm, SW	•	Test-retest Intrarater Interrater	•	
Vibratron II Physitemp Instruments Inc, Clifton, NJ	•	Test-retest Interrater		
Grading Systems (See Table 2) WHO ECOG NCIC-CTC NCI-CTC CTCAE	inconsistent	inconsistent	poor	Inexpensive Clinician/Technician can do Poor agreement among scales
Composite Measures (See Table 4)				
TNS	•	•		Addresses need to include subjective
TNSr	•	•		Additional reliability/ validity needed

- • denotes data available
- • VPT data adapted from (Rapport & Crowther 2003)



CIPN MEASURES - GRADING

Table 2. Grading Scales for Chemotherapy-Induced Peripheral Neuropathy

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

CIPN MEASURES - SELF REPORT

FACT-Taxane (Version 4)

Below is a list of statements that other people with your illness have said are important. By circling one (1) number per line, please indicate how true each statement has been for you during the past 7 days.

PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
I have a lack of energy	0	1	2	3	4
I have nausea	0	1	2		
Because of my physical condition, I have trouble meeting the needs of my family	0	1	2		
I have pain	0	1	2		
I am bothered by side effects of treatment	0	1	2		
I feel ill	0	1	2		
I am forced to spend time in bed	0	1	2		

EORTC QLQ – CIPN20

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have tingling fingers or hands?	1	2	3	4
32. Did you have tingling toes or feet?	1	2	3	4
33. Did you have numbness in your fingers or hands?	1	2	3	4
34. Did you have numbness in your toes or feet?	1	2	3	4
35. Did you have shooting or burning pain in your fingers or hands?	1	2	3	4
36. Did you have shooting or burning pain in your toes or feet?	1	2	3	4

CIPN MEASURES - COMPOSITE

Table 4. Composite Measure: Total Neuropathy Score (TNS)*

Parameter	Score 0	1	2	3	4
Sensory symptoms	None	Limited to fingers or toes	Extend to ankle or wrist	Extend to knee or elbow	Extend to above knee or elbow, functionally disabling
Motor symptoms	None	Slight difficulty	Moderate difficulty	Require help/assistance	Paralysis
Pin sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Vibration sensibility	Normal	Reduced in fingers/toes	Reduced up to wrist/ankle	Reduced up to elbow/knee	Reduced to above elbow/knee
Strength	Normal	Mild weakness (MRC 4)	Moderate weakness (MRC 3)	Severe weakness (MRC 2)	Paralysis (MRC 0 or 1)
Tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	All reflexes reduced	All reflexes absent
Sural amplitude	Normal/reduced <5%	76-95% of LLN	51-75% LLN	26-50% LLN	0-25% LLN
Peroneal amplitude	Normal/reduced <5%	76-95% of LLN	51-75% LLN	26-50% LLN	0-25% of LLN
*Autonomic symptoms	0	1	2	3	4 or 5
*Vibration sensation (QST vibration)% ULN	Normal to 125	126-150	151-200	201-300	>300

RESULTS

1) **CIPN Measures**
- CIPN measures were located and categorized as Objective, Subjective, or Composite Measures. A summary (Table 1) and samples of measures (Tables 2-4) are illustrated. Reliability, validity, sensitivity and specificity data are listed if identified in the literature.

2) **Chemotherapy Trials Reporting CIPN**
- Of the original 58 citations, 22 met criteria. An additional 23 studies were located through scanning references for a total of 45 studies.

- **Cancers Represented:** ovarian (893), cervical (60), endometrial (26), breast (1816), lung (860), colorectal (793), testicular (90), multiple myeloma (65), gastric (56), head and neck (23), gliomas (18), sarcoma (34), "advanced solid tumors" (538)

- **CIPN Incidence:** Range 10-100%; overall mean

- **NTX Chemotherapy Drugs (alone or combined)**
  - Platinum analogs-cisplatin, carboplatin, oxaliplatin
  - Taxanes-paclitaxel, docetaxel
  - Vinca alkaloids-vincristine, vinblastine, etoposide, vinorelbine
  - Thalidomide

Table 5 Peripheral Neuropathy Measures Used in Chemotherapy Clinical Trials*

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 6 Measures Used in Clinical Trials Reporting CIPN

Measure	Total Analy.	Citations
[illegible]	[illegible]	[illegible]

CONCLUSIONS

Based on a review of 45 clinical trials we conclude:

- CIPN incidence varies by study due to differences in drug, dose, patient variables, and measurement techniques. CIPN is often cited as a "dose-limiting toxicity" but no standardized objective and/or subjective criteria exist to determine intolerability. Definitions are varied and imprecise.
- Nerve biopsy is not indicated for routine clinical diagnosis, but may help define neurotoxic mechanisms of new agents.
- Nerve conductions studies, considered the "gold standard" in evaluating polyneuropathy have limited utility in diagnosing CIPN. Studies demonstrate a lack of concurrence between NCS findings and patient report. Its utility has been to initially characterize the neurotoxicity of a specific agent.
- QST represents a wide range of methods with varying reliability, validity, sensitivity and specificity in CIPN. Its utility in routine clinical trial evaluation of CIPN is limited. It is less sensitive than clinical examination.
- Grading systems are used primarily for routine clinical trial measurement of CIPN but lack sensitivity and specificity.
- Self report measures offer an important contribution to CIPN measurement. Several measures are under development and initial reliability & validity reports appear promising.
- Measures (e.g. TNS) which combine subjective symptoms and a standardized neurological examination may provide a more accurate rating of CIPN severity.
- Most clinical trial reports lack the patient's description of symptoms and the effect on functional status.
- Based on the development of other chemotherapy symptom measures, CIPN measurement could be enhanced by qualitative description of symptoms and functional status.

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This research was funded by the Department of Defense Breast Cancer Research Program DAMD17-30-1-0298 and the Oncology Nursing Foundation for Leadership, Information and Research (CLIR).

Appendix C.

Yale University Student Information System

Display Transcript

This is NOT an official transcript. A course for which a grade has not been submitted will appear separately under Courses in Progress.
If your course displays with '***' in the grade column, you must complete a course evaluation or indicate that you choose not to evaluate the course. Click on the link below the asterisks to go to the course evaluation page.

Transfer Credit Institution Credit Courses in Progress

Transcript Data

Registration ID: 1025427

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TRANSFER CREDIT ACCEPTED BY INSTITUTION -Top-

Spring 2003: Dartmouth College

Subject	Course	Title	Grade	Credit Hours
SPRG	2003	Survey Research Methods	CR	3.30

Unofficial Transcript

Spring 2004: Dartmouth College

Subject	Course	Title	Grade	Credit Hours
SPRG	2004	Health Policy 2	CR	3.30

Unofficial Transcript

INSTITUTION CREDIT -Top-

Fall 2002

College: Nursing School

Subject	Course	Title	Grade	Credit Hours	Grade Mode	Instructor
NURS	529	Statistics for Clin Nurs Res	H	0.00	Nursing	M. Funk
NURS	901	Methods for Nursing Research	H	3.00	Nursing	J. Dixon
NURS	913	Conceptual Bas for Nsg Science	H	3.00	Nursing	C. Gilliss K. Knafl
NURS	915	Doc Research Prac I	H	1.00	Nursing	R. McCorkle
NURS	943	Conceptual Basis Self/Fam Mgt	H	3.00	Nursing	R. McCorkle G. Melkus K. Knafl

Unofficial Transcript

Spring 2003

College:					
Subject	Course	Title	Grade	Credit Hours Grade Mode	Instructor
					K. Knafl
NURS	904	Neuro Effects/Breast CancTrtmt	H	3.00 Nursing	R. McCorkle
NURS	915	Doctoral Research Pract II	H	1.00 Nursing	R. McCorkle
NURS	917	Adv Stats for Clin Nurs Resrch	H	3.00 Nursing	G. Knafl
NURS	943	MthlgclIss.StudyMgtHlth&Illns	H	3.00 Nursing	M. Grey
					G. Melkus

Unofficial Transcript

Fall 2003
College: Nursing School

Subject	Course	Title	Grade	Credit Hours Grade Mode	Instructor
NURS	805	Cancer Pharmacology	HP	1.50 Nursing	N. Beaulieu
NURS	903	Measurement of Clin Variables	H	3.00 Nursing	J. Dixon
NURS	907	Dissertation Seminar	YR	0.00 Nursing	R. McCorkle
NURS	915	Doctoral Research Pract II	RE	0.50 Nursing	R. McCorkle
NURS	925	Qualitative Research in Nrsg	H	3.00 Nursing	K. Knafl
NURS	961	Hlth Pol for Pub & Priv Sectrs	HP	3.00 Nursing	S. Cohen

Unofficial Transcript

Spring 2004
College: Nursing School

Subject	Course	Title	Grade	Credit Hours Grade Mode	Instructor
CDE	534	Approaches to Data Management	H	3.00 Nursing	M. Desai
NURS	905	CreatingMethodIssinNursRes	H	3.00 Nursing	J. Dixon
NURS	907	Dissertation Seminar	H	3.00 Nursing	M. Grey
NURS	915	Doctoral Research Pract II	H	0.50 Nursing	R. McCorkle
SOCY	560	Comparative Research Workshop	H	2.00 Nursing	I. Szelenyi
					A. Schrank

Unofficial Transcript

Summer 2004
College: Nursing School

Subject	Course	Title	Grade	Credit Hours Grade Mode	Instructor
NURS	991	Dissertation Advisement	RE	2.00 Nursing	R. McCorkle

Unofficial Transcript

Fall 2004
College: Nursing School

Subject	Course	Title	Grade	Credit Hours Grade Mode	Instructor
NURS	991	Dissertation Advisement	RE	3.00 Nursing	K. Knafl

Unofficial Transcript

COURSES IN PROGRESS -Top-

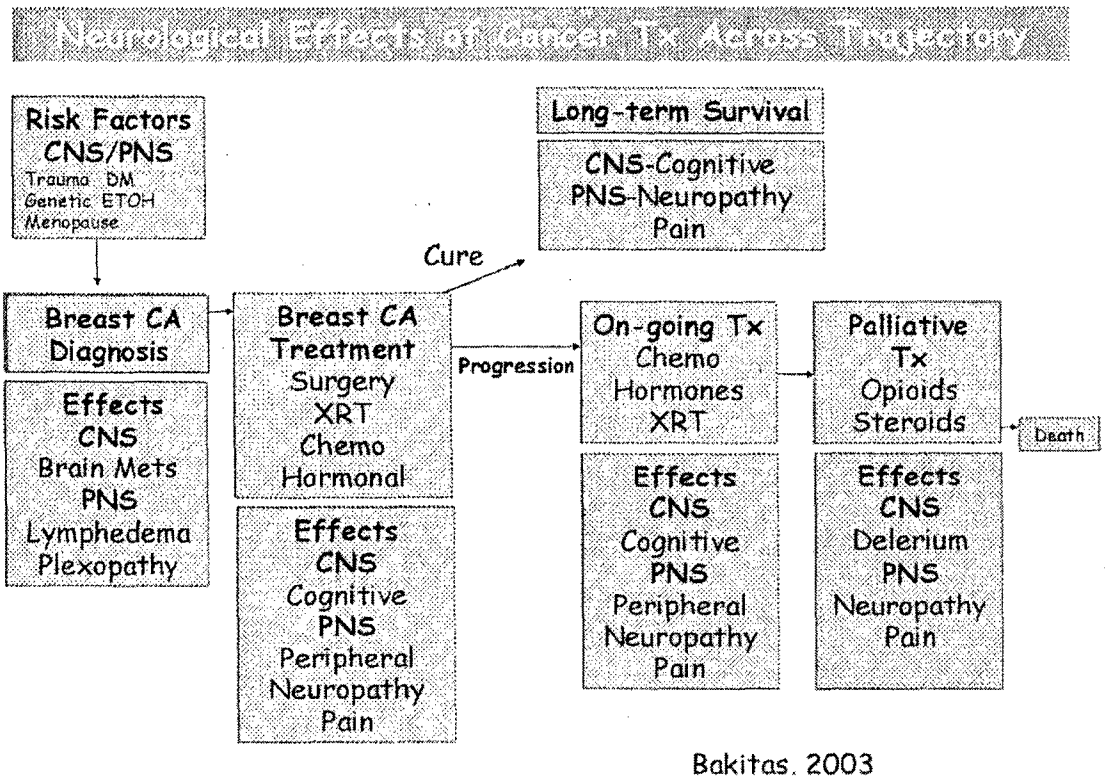
Spring 2005

College: Nursing School

Subject	Course	Title	Credit Hours	Grade Mode	Instructor
NURS	991	Dissertation Advisement	3.00	Nursing	M. Knobf

RELEASE: 5.5

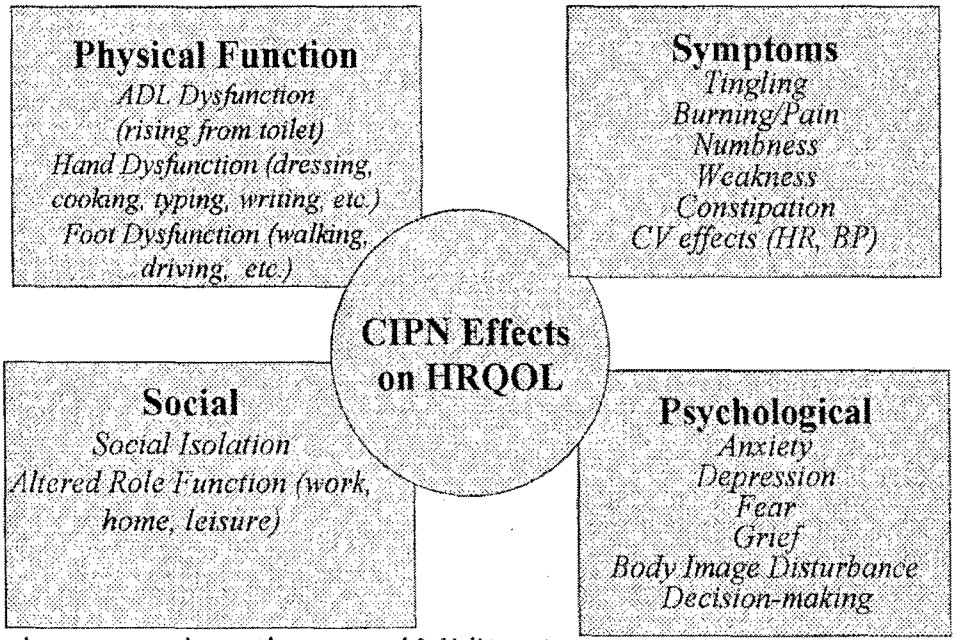
Appendix D.



Bakitas, 2003

Appendix E.

Proposed Model of CIPN Effects on QOL *



*Based on cancer chemotherapy and DM literature

Bakitas 2003

Appendix F.

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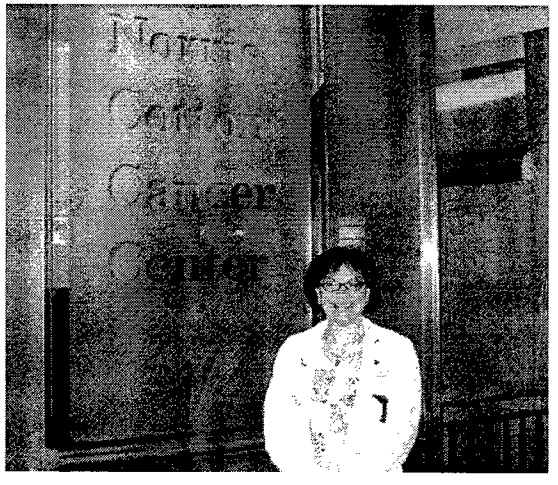
Whom Do I Contact for More Information Or To Enroll In the Study?

Provide your Oncologist or Nurse Practitioner with your name, phone number or email. Marie Bakitas will contact you or you may contact Marie Bakitas by phone or email.

Who Is Conducting This Study?

Marie Bakitas, MS, ARNP
Nurse Practitioner
Norris Cotton Cancer Center,
Dartmouth-Hitchcock Medical Center

Doctoral Candidate
Yale University School of Nursing



NORRIS COTTON CANCER CENTER
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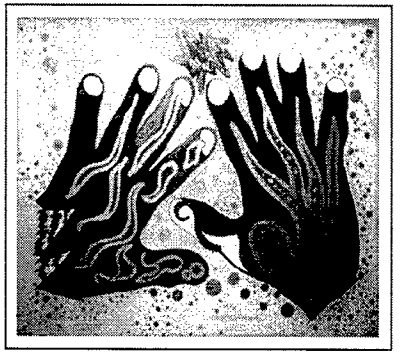

Contact the Study:

Marie Bakitas, MS, ARNP
Phone: 603-653-3524
Email: marie.bakitas@dartmouth.edu

Dartmouth-Hitchcock Medical Center
1 Medical Center Drive
Lebanon, NH 03756

DMS 0505

UNDERSTANDING THE EXPERIENCE OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

WE NEED YOUR HELP WITH A RESEARCH STUDY

Do you have NUMBNESS, TINGLING, BURNING or PAIN in your FEET and/or HANDS from

CANCER CHEMOTHERAPY?

NORRIS COTTON CANCER CENTER
DARTMOUTH-HITCHCOCK MEDICAL CENTER

Am I eligible?

If all of the statements below describe you, you may be eligible to participate in this study.

- If you have **peripheral neuropathy** caused by chemotherapy.
  - Peripheral neuropathy feels like **"pins and needles", burning, numbness, or tingling in the feet and/or hands.**

- If you are receiving **chemotherapy** for any type of cancer.

-Platinums
-cisplatin (Platinol)
-carboplatin (Paraplatin)
-oxaliplatin (Eloxatin)

-Taxanes
-paclitaxel (Taxol)
-docetaxel (Taxotere)

-Plant Alkaloids
-vincristine (Oncovin)
-vinblastine (Velban)
-vinorelbine (Navelbine)

-Other
-thalidomide (Thalidomid)
-bortezomib (Velcade)

- If you did not have neuropathy before receiving chemotherapy.

- If you are 18 years of age or older.

What Is the Study About?

The purpose of the study is to understand what it is like to have the chemotherapy side effect called **peripheral neuropathy**.

What Will I Be Asked To Do?

We will ask you to participate in an **interview** and complete **2 questionnaires.**

- In the interview a researcher will ask you to talk about your symptoms and how these may affect your everyday life.

- The two questionnaires will also ask about your symptoms.

The interview and questionnaires may take about an hour or longer. It will be done at a time and location that is convenient to you.

Why Is This Research Being Done?

This study will help doctors and nurses better understand the symptoms of peripheral neuropathy and how they can affect every-day life. When doctors and nurses understand these symptoms, they may be able to better recognize them. Better recognition may lead to improved treatment, comfort, and function during and after chemotherapy.